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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ANTONIN HOLY,
HANA DVORAKOVA,
ERIK D. A. DE CLERCQ,
JAN M. R. BALZARINI

Appeal No. 2000-1024
Application No. 08/379,551

ON BRIEF

Before WINTERS, GRIMES, and GREEN, Administrative Patent Judges.

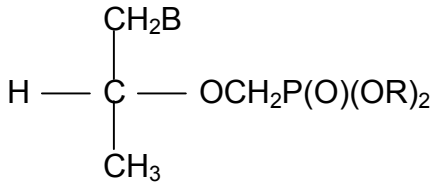
GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 4, 6, 8, 12-19, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94.[1] Claim 1 is representative of the subject matter on appeal, and reads as follows:

[1] According to the Examiner's Answer, claims 49-54, 56-62, 64 and 79 are free of the prior art, with Claim 79 being objected to, and thus these claims are not subject to the instant appeal. See Examiner's Answer, page 2.

1. A compound of the formula:



(IA)

including salts of such compounds, wherein said compound of Formula IA is substantially free of its enantiomer and wherein B is (a) an unsubstituted purine moiety, (b) a substituted purine moiety substituted independently at the 2 and/or 6 and/or 8 position by amino, halogen, hydroxy, alkoxy, alkylamino, dialkylamino, aralkylamino, pyrrolidino, morpholino, piperidino, benzoylamino, azido, mercapto or alkylthio, or (c) the 8-aza analog thereof, and wherein

B is other than a guanine or 2-amino-6-halopurine;

R is H; and aryl in aralkylamino is a 6-10C aromatic group.

Claims 4, 6, 8, 70, 72, 73, 75, 85, 91, 93 and 94 further limit the compound of claim 1. Claims 12-19 are drawn to a method of preparing the compound of claim 1. Claims 45 through 48, 55, 63 and 65 are drawn to specific compounds that fall within the compound of claim 1.

The examiner relies upon the following references:

Hol [*sic*] et al. (Holy (US))	4,808,716	Feb. 28, 1989
Alexander et al. (Alexander)	5,130,427	Jul. 14, 1992
Yu et al. (Yu (US))	5,302,585	Apr. 12, 1994
Vemishetti et al. (Vemishetti)	5,476,938	Dec. 19, 1995
Webb, II et al. (Webb (US))	5,650,510	Jul. 22, 1997

European Patent Applications

Holy et al. (Holy (EP))	0 253 412	Jul. 18, 1986
Webb, II (Webb (EP))	0 269 847	Jun. 08, 1988
Yu et al. (Yu (EP))	0 452 935	Oct. 23, 1991
Starrett et al. (Starrett)	0 481 214	Apr. 22, 1992

Karrer, Organic Chemistry, 2nd English Edition, pp. 92-102 (1946)

The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 11th Edition, Article No. 7868, p. 1247 (1989)

In addition, appellants rely upon the following references:

DeClercq et al. (DeClercq), "Antiviral activity of phosphonylmethoxyalkyl derivatives of purine and pyrimidines," Antiviral Research, Vol. 8, pp. 261-272 (1987)

Holy et al. (Holy (1989)), "Phosphonylmethyl Ethers of Nucleosides and Their Acyclic Analogues," ACS Symposium Series, Vol. 401, pp. 51-71 (1989)

Claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Holy (US), Webb (EP or US), Yu (US or EP), Starrett, Holy (EP) and Karrer. Claims 12-19 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Holy (US), Holy (EP), Webb (EP or US), Vemishetti, Alexander, Yu (US or EP) and the Merck Index. Claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 stand rejected under the judicially created doctrine of obviousness-type double patenting over the claims of Holy (US), U.S. Patent No. 4,808,716 (the '716 patent) as combined with Yu (EP or US), Holy (EP), Starrett and Karrer. Claims 1, 4, 6, 8, 45-48, 55, 63, 65, 72, 73, 75, 85, 91, 93 and 94

stand rejected under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patent No. 5,650,510 (the ’510 patent) as combined with Yu (EP or US), Holy (EP), Starrett and Karrer. Finally, claims 1, 4, 6, 70, 72, 85, 91, 93 and 94 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims of copending Application No. 07/925,610. After careful review of the record and consideration of the issues before us, we reverse all of the rejections of record except the provisional obviousness-type double-patenting rejection of claims 1, 4, 6, 70, 72, 85, 91, 93 and 94 over copending Application No. 07/925,610.

DISCUSSION

Claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Holy (US), Webb (EP or US), Yu (EP or US), Starrett, Holy (EP) and Karrer. In addition, the obviousness-type double patenting rejections over the ’716 patent and the ’510 patent as combined with Yu (EP or US), Holy (EP), Starrett and Karrer are included in the analysis of the rejection over the combination of Holy (US), Webb (EP or US), Yu (EP or US), Starrett, Holy (EP) and Karrer as the rejections state that the claims of the patents are “obvious variant[s] of that claimed herein as discussed in the above 103 rejection.” Examiner’s Answer, page 7. In addition, appellants rely on the patentability of the end product to overcome the rejection of claims 12-19 over the combination of Holy (US), Holy (EP), Webb (EP or US), Vemishetti (US), Alexander (US), Yu (US or EP) and the Merck Index. Thus, that rejection is also encompassed by the following analysis.

Holy (US) is cited by the rejection for teaching a racemic mixture of 2-phosphonomethoxypropyladenine (PMPA). PMPA is included in the range of structures of claim 1. The rejection also references compound 2 in Table 1, as well as a discussion of the applications of the disclosed compounds, such as anti-viral activity, in column 4, lines 14-19 of the Holy (US) patent. The rejection reasons that:

> While the corresponding optical isomer is not particularly disclosed, the claimed R-isomer is held as an obvious variant in view of its very close structural similarity and the fact that one skilled in the art would recognize the existence of such isomers and expect one of a pair to perform better over the other. There is case law regarding the standards of patentability of optical isomers over the corresponding racemic mixture which is on point. See for example, In re Adamson, 125 USPQ 233; Eli Lilly vs. Generix, 174 USPQ 65 regarding the standards of patentability of optical isomers over the corresponding racemic mixture. Note Karrer, cited in Adamson, and applied herein is evidence that it is very well known considerably prior to applicants' effective filing to consider the separation of biologically active racemates in order to determine if one is largely responsible for the desired activity.

Examiner's Answer, page 5.

Webb (EP or US) is apparently cited for teaching derivatives of the compounds as taught by Holy (US). According to the rejection, "Webb does not embrace adenine compound of US Holy but does embrace substituted derivatives thereof having the same sidechain." Examiner's Answer, page 5. Yu (EP or US) is cited for its disclosure of resolution of one of the racemates disclosed by Webb "for elucidation of its antiviral properties," and teaches that the R isomer is "especially effective for treating HIV." Id. at 6.

Holy (EP) was cited for teaching compounds similar to the claimed compounds substituted with different groups, which also have anti-viral activity. Starrett was similarly cited for teaching "that for analogous phosphonate derivatives as claimed herein, substitution with alkyl- on the purine ring system at various ring positions is not a new modification." Id. at 6.

The examiner concludes:

> Thus it would have been obvious to one skilled in the art at the time the instant invention was made to expect instant optical isomers in main claim 1 and claims dependent thereon as well as various 2- and/or 6-substituted purines in independent claims 45-48, 55, 63 to be useful against one or more viruses in view of the close structural similarity and equivalency teachings outlined above.

Id.

The panel would like to initially note that review of the issues on appeal was severely hampered by the lack of claim by claim analysis, i.e., the use of a shot-gun rejection. In rejecting claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 over the combination of Holy (US), Webb (EP or US), Yu, Starrett and Karrer, the examiner apparently cites Holy (EP) and Starrett for their teaching of certain derivatives that are only required in the dependent claims. Moreover, the rejection implies that at a minimum, claim 1 is would have been obvious over Holy alone.

Most tellingly, in the response to appellants' argument that Webb cannot be combined with Holy, the examiner responds that

> Webb is not a secondary reference but rather a primary reference applied for showing additional aspects of appellants' invention as obvious, mainly for its teaching of 2,6 diamino phosphonomethoxypropyl purine, but Webb also teaches and claims bases such as 2-amino purine, 8-substituted guanines (guanine per se is excluded in the instant claims) which are within at least claim 1.

Examiner's Answer, page 9.

If Webb was not to be combined with Holy (US), it should have been separately applied, or at least the examiner should have explicitly stated that Webb was being applied in the alternative. The way in which the rejection was laid out, however, makes it difficult to understand, much less rebut and review.

The burden is on the examiner to set forth a prima facie case of obviousness. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). In order to make a prima facie case of obviousness based on the structural similarity, in this case similarity between the claimed optical isomer and its racemate taught by the prior art, not only must the structural similarity exist, but the prior art must also provide reason or motivation to make the claimed compound. See In re Dillon, 919 F. 2d 688, 692,16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc), In re Mayne, 104 F. 3d 1339, 1341, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997); In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 256 (CCPA 1979). Moreover, the prior art has to enable the ordinary artisan to make the claimed compound. See Payne, 606 F.2d at 314. The rejection over

Holy (US), Webb (EP or US), Yu (EP or US), Starrett, Holy (EP) and Karrer does not meet this criteria and thus fails to set forth a prima facie of obviousness.

In the rejection above, the examiner states with respect to the separation of the racemates of Holy (US) that "it is very well known considerably prior to applicants' effective filing to consider the separation of biologically active racemates in order to determine if one is largely responsible for the desired activity," see Examiner's Answer, page 5, but does not set forth any facts or findings to support the motivational statement, especially since all that is currently being claimed is a single isomer, i.e., the R isomer. See In re Lee, 277 F.3d 1338, 1343-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (in reviewing an obviousness rejection, the court noted that "conclusory statements" as to teaching, suggestion or motivation to arrive at the claimed invention "do not adequately address the issue").

With respect to the additional references cited by the examiner for teaching the various other substituents required by the claims, the only motivation that the examiner provides for making the combination is structural similarity. As noted above, however, structural similarity is not enough, but there must also be some teaching, suggestion, or motivation provided in the prior art to make the combination.

Moreover, appellants also argue that the art teaches away from isolating PMPA or PMPDAP from its isomer. Appellants cite Holy (1989) and DeClercq for teaching that PMPA is an inactive product. See Appeal Brief, pages 19-23. The examiner did not find the teaching away references to be persuasive

because Holy filed and obtained a patent for PMPA and other compounds on the basis that the compounds are antiviral.

Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. See In re Kuderna, 426 F.2d 385, 389, 165 USPQ 575, 578 (CCPA 1970); see also In re Shuman, 361 F.2d 1008, 1012, 150 USPQ 54, 57 (CCPA 1966). In assessing the teachings of the prior art references, the examiner should also consider those disclosures that may teach away from the invention. See In re Geisler, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997).

DeClercq states that PMPA is an "inactive product[ ]". DeClercq, page 264. The examiner dismisses that teaching by arguing that, in context, it appears that DeClercq is referring to the S-isomer. See Examiner's Answer, page 7. When a particular isomer is being referred to by the reference, however, DeClercq seems to indicate as such. Holy (1989) indicates that the replacement of the primary hydroxy group in HPMPA by a methyl group resulted in the loss of activity. See Holy (1989), pages 56-57. Thus, both DeClercq and Holy (1989) teach away from resolving a racemic mixture of PMPA into the currently claimed enantiomer.

In finding that the above prior art references do not teach away from separating a racemic mixture of PMPA into its optically pure isomers, the examiner relies on the Holy (US) patent, apparently bothered by the fact that Holy, who is also an inventor on the instant application, obtained a patent whose claims encompass PMPA. The examiner additionally asserts in support of the

rejection that the patent was obtained because the compounds were shown to have antiviral activity.

While PMPA may be encompassed by the group of structures claimed in the Holy (US) patent, that is not dispositive of the issue of whether PMPA has antiviral activity. A claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph. See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976).

In Table 1 of the Holy (US) patent, specifically referred to by the examiner in rejecting the claims at issue, see Examiner's Answer, page 4, certain chemical characteristics are given for compound 2, i.e., PMPA, but the table does not set forth any biological data. The disclosure of Holy relied upon by the examiner as stating that PMPA has biological activity, i.e., column 4, lines 14-19 of the Holy (US) patent, also does not support the examiner's position. That portion of the patent states:

> Some compounds of the general formula I which are the subject of this invention, are important active components of antiviral drugs. An example of such compound is 9-phosphonylmethoxyethyladenine which exhibits a specific activity against DNA-viruses and Maloney sarcoma (PV 3018-85).

(Emphasis added). Thus, the patent does not assert that all of the compounds have antiviral activity, but that some of the compounds may have antiviral activity. When the disclosure of Holy (US) is read in conjunction with the teachings of DeClercq and Holy (1989), which specifically address PMPA,

teaching that compounds such as PMPA do not have antiviral activity, the prior art, when read as a whole, teaches away from separating a racemic mixture of PMPA into its optically pure isomers.

In addition, the examiner also relies upon Adamson and Eli Lilly as apparently standing for the proposition that an optically pure form of a compound is per se obvious over a disclosure of a racemic mixture of the compound. See Examiner's Answer, page 8 ("The motivation to resolve the racemate of Holy is fully supported by the case law previously cited dealing with racemates vs. individual optical isomers."). One cannot rely on case law alone, however, to provide the motivation to modify a prior art compound. "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." In re Rouffet, 149 F.3d 1350, 1356, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998) (citations omitted). In this case, the prior art as a whole, as discussed above, teaches away from making the modification as suggested by the examiner.

Claims 1, 4, 6, 70, 72, 85, 91, 93 and 94 stand provisionally rejected over the claims of co-pending Application No. 07/925,610. As appellants do not present any arguments as to why the rejection is improper, but instead note their intent to file a terminal disclaimer once the copending case is sent to issue, this rejection is affirmed.

CONCLUSION

The rejection of claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 over the combination of Holy (US), Webb (EP or US), Yu (EP or US), Starrett, Holy (EP) and Karrer is reversed. For the same reasons, the obviousness-type double patenting rejections over the ’716 patent and the ’510 patent as combined with Yu (EP or US), Holy (EP), Starrett and Karrer, and the rejection of claims 12-19 over the combination of Holy (EP), Webb (EP or US), Vemishetti, Alexander, Yu (US or EP) and the Merck Index, are also reversed. Finally, the provisional rejection of claims 1, 4, 6, 70, 72, 85, 91, 93 and 94 over the claims of co-pending application No. 07/925,610 is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART; REVERSED-IN-PART

SHERMAN D. WINTERS Administrative Patent Judge	)
ERIC GRIMES Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
LORA M. GREEN Administrative Patent Judge	)

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